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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,657	05/04/2001	Harry M. Meade	GTC-21	9001

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EXAMINER	
HAMA, JOANNE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/849,657	MEADE ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,14-19,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,14-19,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the First Action on the Merits August 2, 2005. Claims 10 and 15-19 are amended. Claims 25 and 26 are new. Claims 1-9, 11-13 are cancelled. Claims 10, 14-19, 25, and 26 are under consideration.

Specification

Applicant has filed corrections to the specification. The Examiner acknowledges that the amendments in the specification were to correct the name of the author from "Colowick et al" to "Wu and Grossman, Eds." and incorporate the year "1996 to the cited White et al. article.

Information Disclosure Statement

The Examiner acknowledges the corrections made by the Applicant to incorporate the correct author from "Colowick et al." to "Wu and Grossman, Eds." and to include a year to the article by White et al. As stated in the Office Action of February 10, 2005, these references have been considered. Because this corrected copy of the IDS is a duplicate of the one sent December 13, 2004, the Examiner has indicated the previously considered references as duplicates, "dup."

The information disclosure statement filed May 23, 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the

application file, but the information referred to therein has not been considered. While the Kuwajima et al., and Wu et al., references have been considered, no copy was received for the Hegenhart reference. In addition to this, the references Myers et al. and Hegnenhart references are not in proper citation format. These references have been lined through and were not considered.

The information disclosure statement filed May 23, 2005 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because a the Hegenhart reference is missing and the Hegenehart and Meyers et al. references are not in proper citation format. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Withdrawn Rejections

35 U.S.C. § 101

Applicant's arguments, see page 6 of Applicant's response, filed August 2, 2005, with respect to the rejection of claims 10, 16-19 have been fully considered and are persuasive. Applicant has amended the claims to include the phrase, "non-human." The rejection of claims 10, 16-19 has been withdrawn.

35 U.S.C. § 102(b)

Applicant's arguments, see page 9 of Applicant's response, filed August 2, 2005, with respect to the rejection of claim 10 have been fully considered and are persuasive. Applicant has amended the claim to making a preparation in the milk of a non-human mammal. This was not taught by Hering et al., which teaches recombinant decorin made in bacteria. The rejection of claim 10 has been withdrawn.

New and Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 26 is newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 26 introduces new matter because nothing in the specification or claims as originally filed teach or are drawn to a method of making a preparation of recombinant human decorin from the milk of a non-human mammal, further comprising using a vector to amplify a recombinant human decorin nucleic acid sequence. Nothing in the

specification indicates that a second vector is introduced to a non-human mammal such that the nucleic acid sequence encoding human decorin is amplified.

Claims 10, 14-19, 25 remain rejected in modified form under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method of making milk comprising transgenic human decorin obtained from a transgenic mouse comprised of an expression cassette of a goat beta-casein promoter operably linked to the nucleotide sequence encoding human decorin stably integrated in its genome

and

for a method of making transgenic human decorin in E. coli, S. cerevisiae, and S. pombe and obtaining a preparation from E. coli, S. cerevisiae, and S. pombe, and

a transgenic mouse comprising in its genome a transgene construct comprising a nucleic acid sequence encoding human decorin operably linked to a goat beta-casein promoter, wherein the mouse expresses human decorin in its milk

does not reasonably provide enablement for

a method of making any preparation of recombinant human decorin from the milk of any non-human mammal comprising:

providing any non-human mammal, which includes any transgene which directs the expression of decorin,

allowing the transgene to be expressed in the non-human mammal, and

recovering any preparation of transgenically produced decorin, from the non-human mammal or from any product produced by the non-human mammal

and

a transgenic non-human mammal, other than mouse, comprising in its genome a transgene construct comprising a nucleic acid sequence encoding human decorin operably linked to a goat beta-casein promoter, wherein the non-human mammal expresses human decorin in its milk.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record, February 10, 2005.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

With regards to the claimed invention being drawn to a method of making a preparation of recombinant human decorin comprising a step of including any transgene which directs the expression of decorin, the claims broadly encompass any method of delivery of the transgene. In addition to choice of vector, this includes route of delivery, and cell types comprising the transgene. While the specification teaches that decorin was obtained from transgenic mice comprising a transgene construct comprising a nucleic acid sequence encoding human decorin operably linked to a goat beta-casein promoter, wherein the transgene is stably integrated in the mouse's genome, wherein the mice were obtained by pronuclear injection, the art teaches that transgenes can be introduced in a plasmid or in a viral vector, i.e. gene therapy. While gene therapy has been one way of introducing transgenes, the art teaches that it is an unpredictable way of obtaining recombinant protein. The art provides an example wherein artisans use a plasmid construct to treat a disease, but also illustrate that it is not a viable way of obtaining large amounts of decorin protein. The art at the time of filing teaches that decorin is a secretable protein and when injected into the circulation, is rapidly taken up by kidney, liver, and lung (Isaka et al., 1996, Nature Medicine, 2: 418-423, see IDS, pages 418, 2nd col., 3rd parag to page 419, 1st col., 1st parag). The art teaches that mice were administered an expression vector comprising a nucleic acid sequence encoding rat decorin operably linked to a chicken beta-actin promoter. The plasmid was injected

into the gluteal muscle of rats (Isaka et al., pages 419, parag. under "Gene transfer into normal rats" and page 421, under "Expression vectors"). While Isaka et al. observed that there was a therapeutic effect resulting from decorin expression, wherein proteinuria, a hallmark of the clinical severity of glomerulonephritis, was significantly reduced in decorin-treated rats (Isaka et al., page 419, under "Effect of decorin transfection on proteinuria"), Isaka et al. teach that, "at no time were we able to detect decorin in the plasma of control or decorin-transfected rats. This result was anticipated because of the short half-life of circulating decorin and the known technical difficulty in measuring proteoglycans using immunochemical methods (Isaka, et al., page 419, under "Gene transfer in normal rats"). The art illustrates a few points that do not enable the claims for its full breadth. First, the claims broadly encompass any method of introducing a transgene that directs the expression of decorin. As illustrated by Isaka, et al., a method comprising injection of a plasmid into muscle is viable for treating glomerulonephritis, but is not a viable way of harvesting recombinant decorin protein. Second, the art teaches that while cells, such as muscle cells, can be used to make secretable protein, the art teaches that decorin in the circulatory system is highly unstable. No guidance was provided as to how to make decorin stable such it survives the circulatory system, makes its way into breast tissue and is deposited in milk. Third, the art teaches that decorin is rapidly taken up by kidney, liver, and lung. However, no guidance was provided whether breast tissue could take up decorin, nor was guidance provided that upon uptake of decorin from circulation in the blood by breast tissue that it would be deposited in milk. Fourth, Isaka et al. teach that recombinant decorin in

plasma is undetectable because decorin is unstable. Therefore, while the claims are drawn obtaining decorin from the non-human mammal or from any product produced by the non-human mammal (e.g. urine, plasma), the art teaches that not all sources of the non-human mammal are viable places to find recombinant decorin because decorin is unstable in these tissues and fluids. In addition to the issues raised by the teachings of Isaka et al., the claimed invention is broad for the use of viral vectors and administration of a transgene construct via gene therapy. With regards to this issue, the art teaches that viral vectors are unpredictable. In the case of retroviral vectors, while one great benefit of using a retroviral vector is that it integrates stably into the host's genome and hold the promise of life-long expression of the gene product (Somia and Verma, 2000, Nature Reviews, 1:, 91-99, page 91, 2nd parag. under "A survey of viral vectors"). However, because a retroviral vector integrates into a genome randomly, a retroviral vector could integrate into a site that is transcriptionally inactive or is under the control of a suppressor. As such, the transgene would not be expressed. In the case of using an adenoviral vector, the art teaches that adenoviral expression is transient. The art teaches that this is because the humoral and cellular response of the host's immune system destroys the adenovirus and prevents repeat administration of the adenovirus (Somia and Verma, page 94, under "Immune response: the bane of gene therapy" to page 95, 1st col., 1st parag.). In addition to the difficulties associated with selecting a vector, the art teaches that there are difficulties with regards to route of administration of the transgene construct. In the case of administering a construct intravenously, the art teaches that plasmid injected intravenously undergoes degradation and is rapidly

eliminated from the plasma due to rapid uptake by the liver (Kawabata et al., 1995, Pharmaceutical Research, 12: 825-830, abstract). In the case of administering the construct intramuscullary, Isaka et al. (above) teach that while muscle cells transfected with construct could secrete decorin, they teach that very little decorin could be obtained from the plasma. Thus, while the claimed invention encompasses these embodiments, the specification does not provide guidance on how to overcome these hurdles in the art. Therefore, for these reasons, the specification does not provide guidance for an artisan to practice the claimed invention for its full breadth.

The claimed invention broadly encompasses a method of making a preparation of recombinant human decorin from milk of a non-human mammal, wherein the transgene construct comprises a nucleic acid sequence encoding human decorin operably linked to any promoter. As discussed in the Office Action of February 10, 2005, there is unpredictability in obtaining a regulatory element (e.g. promoter) from one species of animal and having it be active in another species of animal. For example, Cowan et al. (2003, Xenotransplantation, 10: 223-231) teach that promoters of three human genes, ICAM-2, hCRPs, and PECAM-1, which are predominantly expressed in vascular endothelium in mice and pigs. When tissue specific expression was measured, it was found that while mice showed a distinct expression profile of the three human genes, the tissue expression profiles of the three human gene promoters were distinctly different in pigs. The authors concluded that "promoter performance in mice and pigs was not equivalent," and that "the weak expression driven by the human ICAM-2 promoter in pigs relative to mice suggests the need for additional regulatory

elements to achieve species-specific gene expression in pigs (Cowan et al., abstract)." While the specification teaches transgenic mice comprising a transgene construct comprising a nucleic acid sequence encoding human decorin operably linked to a goat beta-casein promoter, wherein decorin protein was detected in milk, the specification, in light of the teachings in the art, does not teach how to obtain promoters such that mammalian promoters predictably expresses in other transgenic mammals. Similarly, as illustrated by Cowan et al., the art teaches unpredictability in obtaining any promoter and know that it would have activity in other species of organism. Thus, while the specification teaches transgenic mice comprising a transgene construct comprising a nucleic acid sequence encoding human decorin operably linked to a goat beta-casein promoter, wherein the transgene construct is stably integrated in the genome, the art, Cowan et al., provides teachings such that the specification does not enable an artisan to practice the full scope of any promoter.

Claim 19 broadly claims a transgenic non-human organism which expresses a transgenic decorin and from which a transgenic preparation of decorin can be obtained. At the time of filing, the art teaches that bacteria was one way of making expressing recombinant decorin (Hering et al., 1996, Analytical Biochemistry, 240, 98-108). The specification also provides an example of obtaining recombinant decorin in milk of transgenic mice (specification, Table 1, page 53). While the specification teaches that large amounts of human decorin can be obtained from the milk of transgenic mice comprising a stably integrated transgene construct comprising a nucleic acid sequence encoding human decorin operably linked to a goat beta-casein promoter, the art

teaches that rats injected in muscle with a transgene construct comprising a nucleic acid sequence encoding rat decorin operably linked to a chicken beta-actin promoter does not secrete detectable levels of decorin into the plasma (Isaka et al., see above). In light of the fact that Isaka et al. teach that rat decorin is not detectable in plasma and is not a viable way of harvesting large amounts of decorin protein, an artisan cannot predict that any region of any organism, such as a tree or a snake is a necessarily viable site for expressing and obtaining detectable amounts of decorin. Thus, while the specification teaches transgenic mice comprising a transgene construct comprising a nucleic acid sequence encoding human decorin operably linked to a goat beta-casein promoter, the specification does not provide any guidance as to what other organisms could produce recombinant decorin such that a preparation of decorin could be obtained.

In view of the lack of guidance, working examples, breadth of the claims, and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Response to Arguments

Applicant's arguments, pages 6-9 of Applicant's response, filed August 2, 2005 have been fully considered but they are not persuasive.

The Applicant asserts that it is not required to teach every detail of the invention or to perform the function of a technical production manual/specification and that the specification need only explain how to make and use the invention without requiring an

inordinate amount of experimentation (Applicant's response, page 7). While the Applicant provides this assertion, the Examiner disagrees because as illustrated above, claims encompass embodiments of transgenesis and gene therapy which the art teaches is unpredictable. The claimed invention encompasses a transgenic non-human mammal is comprised of any transgene that directs the expression of decorin, wherein decorin is obtained from the milk of the transgenic non-human mammal. As described above, the embodiments of any transgene include issues of DNA vector, delivery of vector, expression ability of the vector, and promoter activity of the vector. These are issues that the art teaches are unpredictable and must be determined empirically. The art also teaches that obtaining large amounts of recombinant decorin (other than from bacteria) is unpredictable. Isaka et al. teaches that decorin is unstable in plasma. In light of the fact that decorin is unstable, an artisan cannot predict that decorin can be expressed and obtained from other body fluids (e.g. urine) or other organs (e.g. purified from kidney). In addition to this issue, claim 19 is broad for any non-human organism that expresses decorin and from which a transgenic preparation of decorin is obtained. Again, in light of the fact that decorin is unstable, an artisan would need to empirically determine what organisms and what fluid or part of the organism would be a viable site for decorin expression such that decorin can be obtained. This would require undue experimentation because no guidance was provided as to what parameters one would use to obtain stable decorin or what conditions should decorin be expressed in such that it does not degrade. Thus, while the Applicant asserts that not every detail needs to be taught in order to practice the claimed invention, the art indicates that to be

enabled for the scope of the claimed invention, one would need to address many unpredictable issues in the art of transgenesis and recombinant protein expression that an artisan would need to perform undue amounts of experimentation in order to be enabled for its fullest breadth.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 26 is confusing. Claim 26 is drawn to a method further comprising using a vector to amplify a nucleic acid sequence encoding human decorin. On one reading of the claims, the "vector" could be read as a term used in parasitology for various pathogens. However, nothing in the specification or art teaches that administration of bacteria or yeast to a transgenic non-human mammal, aids in amplifying a nucleic acid sequence. Alternatively, a "vector" in molecular biology is a plasmid. However, the claim then does not make sense because a DNA plasmid cannot be bacteria or yeast. Claim 26 is also drawn to amplification of a human "decoring" nucleic acid sequence. This appears to be a typographical error.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 19 is newly rejected under 35 U.S.C. 102(b) as being anticipated by Hering et al, 1996, Analytical Biochemistry, 240: 98-108.

Claim 19 is to a transgenic non-human organism which expresses transgenic decorin and from which a transgenic preparation of decorin can be obtained.

Hering et al. teach how to express bovine decorin in bacterial cells. The nucleotide sequence encoding bovine decorin was inserted into an expression vector pMal-c (page 100, first column, lines 20-21). The vector was then transformed into *E. coli* TB-1, TOPP, or XL1-blue cells, grown in culture, and induced with IPTG. Bacteria were then lysed (page 101, first column, first paragraph under "Preparative Induction, Refolding, and Purification of MBP-Decorin," lines 14-21), the inclusion bodies were dissolved (page 101, first column, first paragraph under "Preparative Induction, Refolding, and Purification of MBP-Decorin," lines 25-28), and the protein was renatured (page 101, first column, second paragraph under "Preparative Induction, Refolding, and Purification of MBP-Decorin," to second column, first three paragraphs).

Therefore, Hering et al. anticipate claim 19.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10, 14, 16-19, and 25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Houdebine et al. (U.S. Patent 5,965,788, patented October 12, 1999) in view of Krusius and Ruoslahti (1986, PNAS, USA, 83: 7683-7687, see IDS), Mann et al. (1990, JBC, 265: 5317-5323) and Roberts et al. (1992, Gene 121: 255-262) for reasons of record, February 10, 2005.

It is noted that claim 15 was inadvertently included in the rejection during the First Action. Claim 15 is not rejected under 35 U.S.C. 103(a).

Applicant's arguments filed August 2, 2005, pages 11-14 of Applicant's response, have been fully considered but they are not persuasive.

The Applicant points out that their claimed invention provides for the production and secretion of specific hormonally induced proteins (e.g. milk and milk proteins) in incredibly high concentration and pushes them out of the system of a whole animal in a regular reliable amount (Applicant's response, page 12). The Applicant asserts that none of the references cited by the Examiner provide sufficient guidance along this line to negative patentability (Applicant's response, page 12). With regards to this assertion, the Examiner disagrees. The Examiner has indicated that Houdebine et al. teach a method of preparing a protein of interest in the milk of a transgenic mouse (First Action, February 10, 2005, page 11). Houdebine et al. teach that mice comprising a transgene construct comprising a nucleic acid sequence encoding human growth hormone operatively linked to a rabbit WAP gene produced human growth hormone protein in milk. Houdebine et al. teach that milk-expressed transgenic protein is abundant in

supply and tends to be properly post-translationally modified. The Examiner points out that while Houdebine et al. teach human growth hormone expression in mouse milk, they do not teach decorin protein, nor do they teach the promoter of goat beta-casein. The Examiner points out that Krusius and Ruoslahti teach the nucleotide sequence of human decorin and that Mann et al. teach the sequence of decorin, wherein the glycosaminoglycan attachment site is eliminated. Roberts et al. teach that the goat beta-casein gene encodes the most abundant protein of goat milk. Further, Roberts et al. teach that compared to transgenic mice comprised of a rat beta-casein gene, the mice expressing the goat beta-casein gene expressed the goat gene consistently higher than the rat counterpart. Thus, these teachings, collectively, provide guidance and motivate an artisan to arrive at the claimed invention.

The Applicant also provides an argument that the prior art cited by the Examiner is simply insufficient to render the amended claims unpatentable and indicates that Ruoslahti et al. relates to the use of cell culture/*in vitro* derived decorin (Applicant's response, page 13-14). It is noted that while the Applicant refers to the citation as "Ruoslahti et al.," the cited reference was in the 103 was Kruisus and Ruoslahti. For purposes of discussion, it is assumed that this "Ruoslahti et al." refers to "Kruisus and Ruoslahti." With regards to these assertions, the Examiner disagrees because as discussed above, the teachings in the art provide guidance for an artisan to arrive at the claimed invention. While the Applicant points out the insufficiencies of Ruoslahti, et al., no discussion was provided regarding the insufficiencies of the other cited references. Further, while the Applicant points out the insufficiencies of Ruoslahti, et al., it should be

pointed out that Ruoslahti et al. was not relied upon as a 102 rejection. Rather, Ruoslahti et al. was relied upon as providing a teaching, i.e., the sequence of human decorin, such that an artisan, with the combined teachings of Houdebine, et al., Mann et al., and Roberts et al. would arrive at the claimed invention.

Thus, for these reasons, claims 10, 14, 16-19, and 25 remain rejected.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

(EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER